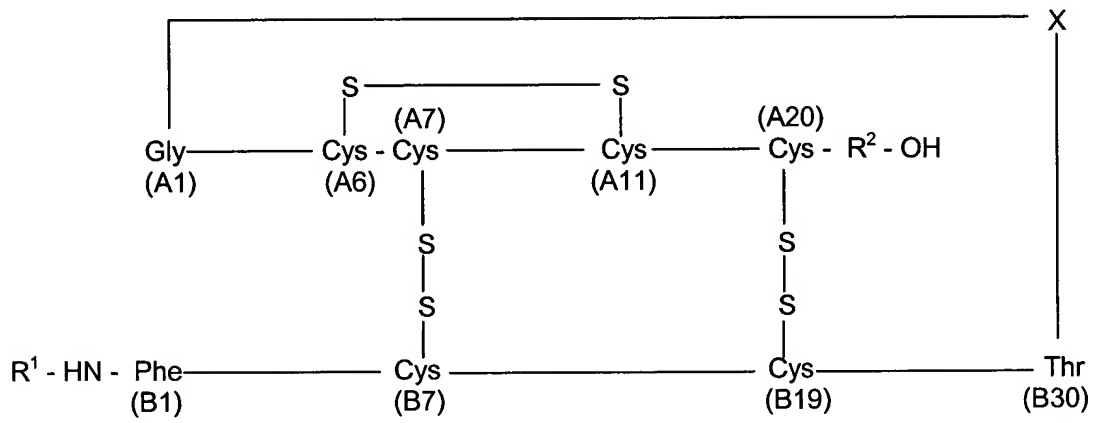
We claim:

1. A method for the chromatographic purification of preproinsulin of the formula 1,



R^1-B1-B30-X-A1-A20-R^2 (1)

wherein

X a) is a genetically encodable amino acid residue or
b) is a peptide having from 2 to 35 amino acid residues, which starts and ends with in each case a basic amino acid residue, in particular Arg, and which, if it consists of more than 3 amino acid residues, starts and ends with in each case two basic amino acid residues, in particular Arg and/or Lys,

R^1 a) is hydrogen,
b) is a genetically encodable amino acid residue or
c) is a peptide having from 2 to 15 amino acid residues,

R^2 is a genetically encodable amino acid residue, and

and the residues A1 – A20 correspond to the amino acid sequence of the A chain of human insulin or of an insulin analog and the residues B1 – B30

correspond to the amino acid sequence of the B chain of human insulin or of an insulin analog;

wherein said method for chromatographic purification of preproinsulin comprises:
removing higher molecular weight substances from an aqueous solution of said preproinsulin by means of a first chromatography on an anion exchanger in flow-through mode and a subsequent second chromatography on a cation exchanger in adsorption mode.

2. A method for the chromatographic purification of the genetically engineered preproinsulin of formula 1 of Claim 1, wherein said preproinsulin has the following amino acid sequence:

Ala-Thr-Thr-Ser-Thr-Gly-Asn-Ser-Ala-Arg-Phe-Val-Asn-Gln-His-Leu-Cys-Gly-Ser-His-Leu-Val-Glu-Ala-Leu-Tyr-Leu-Val-Cys-Gly-Glu-Arg-Gly-Phe-Phe-Tyr-Thr-Pro-Lys-Thr-Arg-Arg-Glu-Ala-Glu-Asp-Pro-Gln-Val-Gly-Gln-Val-Glu-Leu-Gly-Gly-Gly-Pro-Gly-Ala-Gly-Ser-Leu-Gln-Pro-Leu-Ala-Leu-Glu-Gly-Ser-Leu-Gln-Lys-Arg-Gly-Ile-Val-Glu-Gln-Cys-Cys-Thr-Ser-Ile-Cys-Ser-Leu-Tyr-Gln-Leu-Glu-Asn-Tyr-Cys-Asn (SEQ ID NO: 2).

3. A method for the chromatographic purification of the genetically engineered preproinsulin of formula 1 of Claim 1, wherein said preproinsulin has the following amino acid sequence:

Ala-Thr-Thr-Ser-Thr-Gly-Asn-Ser-Ala-Arg-Phe-Val-Asn-Gln-His-Leu-Cys-Gly-Ser-His-Leu-Val-Glu-Ala-Leu-Tyr-Leu-Val-Cys-Gly-Glu-Arg-Gly-Phe-Phe-Tyr-Thr-Pro-Lys-Thr-Arg-Arg-Glu-Ala-Glu-Asp-Pro-Gln-Val-Gly-Gln-Val-Glu-Leu-Gly-Gly-Gly-Pro-Gly-Ala-Gly-Ser-Leu-Gln-Pro-Leu-Ala-Leu-Glu-Gly-Ser-Leu-Gln-Lys-Arg-Gly-Ile-Val-Glu-Gln-Cys-Cys-Thr-Ser-Ile-Cys-Ser-Leu-Tyr-Gln-Leu-Glu-Asn-Tyr-Cys-Gly (SEQ ID NO: 3).

4. A method for the chromatographic purification of the genetically engineered preproinsulin of formula 1 of Claim 1, wherein said preproinsulin has the following amino acid sequence:

Ala-Thr-Thr-Ser-Thr-Gly-Asn-Ser-Ala-Arg-Phe-Val-Lys-Gln-His-Leu-Cys-Gly-Ser-His-Leu-Val-Glu-Ala-Leu-Tyr-Leu-Val-Cys-Gly-Glu-Arg-Gly-Phe-Phe-Tyr-Thr-Pro-Glu-Thr-Arg- Asp-Val-Pro-Gln-Val-Glu-Leu-Gly-Gly-Gly-Pro-Gly-Ala-Gly-Ser-Leu-Gln-Pro-Leu-Ala-Leu-Glu-Gly-Ser-Leu-Gln-Lys-Arg-Gly-Ile-Val-Glu-Gln-Cys-Cys-Thr-Ser-Ile-Cys-Ser-Leu-Tyr-Gln-Leu-Glu-Asn-Tyr-Cys-Asn (SEQ ID NO: 4).

5. Use of the method of Claim 1 to separate foreign substances from said aqueous solution of preproinsulin which induce insulin denaturation.

6. The method of Claim 1 wherein said second chromatography is carried out at a pH of from 3.0 to 5.5.

7. The method of Claim 1 wherein said second chromatography is carried out under a pressure of from 1 to 30 bar.

8. A method for preparing insulin by expressing nonfolded preproinsulin, comprising the steps of:

a) fermentation of genetically modified microorganisms which express nonfolded preproinsulin,

b) harvesting the microorganisms and cell disruption,

c) isolating the inclusion bodies containing undissolved, nonfolded preproinsulin,

d) dissolving the preproinsulin with correct folding of the peptide chain and simultaneous closure of the disulfide bridges to give preproinsulin, and subsequently carrying out the chromatographic purification method of claim 1,

e) enzymic cleavage of preproinsulin to give human insulin,

f) purification of human insulin,

g) crystallization of human insulin and drying.